UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/237,291	01/25/1999	JUDY CAROL YOUNG	SYS-2068	9391

1095 7590 06/02/2004

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 430/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
LACOURCIERE, KAREN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/237,291	YOUNG ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-20,23-27,31-34,37-43,46-50 and 52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20,23-27,31-34,37-43,46-50 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Drawings

The drawings were received on March 8, 2004. These drawings are acceptable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-20, 23-27, 31-34, 37-43, 46-50 and 52 are maintained as rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al. (US Patent 5,665,557), Nakahata (US Patent 5,861,315), Hoffman et al. (US Patent 5,744,361), Fei et al. (US Patent 5,635,387) or Davis et al. (US Patent 5,599,703), in view of Ku et al, Kobayashi et al, Ramsfjell et al (IDS Reference AK), Ohmizono et al, Szilvassy et al, Escary et al., or Bodine et al, and further in view of Tushinski et al (IDS Reference AN),

Fletcher et al., Bello-Fernandez et al, or Hatzfeld et al. and Hanenburg et al. (Nature Medicine, Vol. 2, No.8) or Heneburg et al. (IDS reference AR) for the reasons of record set forth in the prior Office actions.

Response to Arguments

Applicant's arguments filed March 8, 2004 have been fully considered but they are not persuasive.

In response to the rejection of record under 35 USC 103, Applicant argues that none of the references cited demonstrate that the cells that proliferated were pluripotent, as required by the claims. These arguments have not been found to be persuasive, as discussed in detail below.

Applicant argues that Ku et al. is not an applicable reference because the reference uses murine hematopoietic progenitors and the skilled artisan would not have any reasonable expectation to extrapolate results from murine cells to human cells. This is not found to be persuasive because human and mouse hematopoietic cells are very similar and it is typical for the skilled artisan to extrapolate results in murine cells to then practice the same methods in human cells. Applicant has not provided any specific reasons why the skilled artisan would not reasonably expect to see the same results in human hematopoietic cells as observed in murine cells.

Applicant further argues that the claims require the presence of at least an mpl ligand and a flt3 ligand, but the reference Ku et al. teaches using TPO (an mpl ligand) and SF (a c-kit ligand) and, therefore, does not meet all the limitations of the claims. This is not found to be persuasive because Ku et al. also taught the combined use of

mpl ligand and flt3 ligand on page 4124 as follows: first they taught that the Mpl ligand is the "physiological regulator of thrombopoiesis and is identical to thrombopoietin (TPO).", then they taught that "we have observed that TPO can support formation of multilineage colonies from marrow cells of 5-fluorouracil (5-FU)-treated mice in synergy with Steel factor (SF, Kit ligand) or interleukin-3 (IL-3). This observation is in agreement with the of Alexander et al. that Mpl knockout mice have reduced number of mulitpotential progenitors relative to wild-type mice.", next they taught that experiments using soluble TPO receptor (sTPOR) on multilineage colony formation supported by the combination of TPO and SF does not suppress colony formation from primitive progenitors, and more pertinent to the instant claims, that sTPOR, in synergy with SF or F1t3/F1k2 ligand (FL), can directly stimulate colony formation from primitive progenitors" and that "these observations may be important for in vitro manipulation of hematopoietic stem cells." Thus, they do specifically teach the combination of mpl ligand/TPO and f1t3 ligand for use in stimulation of hematopoietic stem cell growth, as well as in combination with other cytokines.

Additionally, the secondary references cited in the rejection of record further teach the claimed combination. For example, Kobayshi et al. further taught use of the combination of FL and TPO (see abstract) on growth of CD34+ cells. Furthermore, Ohmizono et al. taught in the abstract that "we studied the effects of stem cell factor (SCF) and flt3 ligand (FL) on the ex vivo expansion of human umbilical cord blood (CB)-derived CD34+ cells in combination with various cytokines, including interleukin (IL-3, IL-6, IL-11), and c-Mpl ligand (thrombopoietin, TPO), in a short-term serum free liquid

suspension culture system." They thus also taught the use of the combination of flt3 and mpl.

Ramsfjell et al. (abstract) further taught that "we also demonstrate that the majority of TPO-recruited CD34+CD38- progenitor cells have a multilineage differentiation potential, and that TPO promotes prolonged expansion of multipotent progenitors. Specifically, whereas progenitor cells were reduced in cultures containing only KL+FL, addition of TPO resulted in 40-fold expansion of multipotent progenitors following a 14-day incubation."

Applicant argues that none of the experiments performed in Ku et al. utilize the combination of mpl ligand and flt3 ligand. This is not persuasive because although Ku et al. does not actually reduce the claimed methods to practice, Ku et al. in combination with the secondary references clearly teaches the combination.

Applicant argues that the experiments disclosed in Ku et al. the treatments resulted in differentiation and multilineage colonies and identifiable megakaryocytes. Applicant argues that these results are opposite to that of the present invention, which allows proliferation of pluripotent stem cells without differentiation. This is not found to be persuasive because the term pluripotent would not exclude the possibility of some differentiated cells or cells with multilineage potential, as taught in Ku et al. and in the secondary references. Applicant argues a difference in the experiments presented in the specification, as compared to experiments disclosed in Ku et al., but the determination of obviousness is based on the methods claimed, not on the examples provided in the specification.

Applicant argues that the term pluripotent has been defined as cells which are capable of differentiating into any cell of the hematopoietic system and that multipotent cells are capable of becoming only a subset of cell types. Applicant argues that none of the references cited assess whether or not the cells can support pluripotent cell proliferation and the assays employed suggest that they did not successfully obtain proliferating pluripotent cells. Applicant argues that they have assessed their cell lines and determined that their methods result in proliferation of the pluripotent cells and retention of their pluripotency. This is not found to be persuasive because the fact that the references did not assess their cell lines using the assays disclosed in the instant application does not mean they did not achieve proliferation of pluripotent cells. The cited references do provide the limitations of the claimed methods, as well as motivation to practice these methods and a reasonable expectation that the skilled artisan would be able to achieve proliferation of the cell lines, as claimed. Applicant seems to be relying on unexpected results to overcome the rejection, however, these results do not appear to be applicable to the broad scope of the methods claimed.

Applicant argues that none of the cited references use the Thy-1+ marker to further purify their cells and therefore it would be expected that the starting frequency of true pluripotent cells to be lower than shown in the instant Application and there is a real possibility that there are no pluripotent cells present. Applicant argues that the observed proliferation and lineage restricted differentiation could be attributable to selective proliferation and differentiation of more committed progenitors or to the absence of true pluripotent cells. This is not persuasive because the claims do not

require a step wherein the cells are purified using the Thy-1+ marker, Applicant is arguing a limitation not found in the claims. Although the cell populations used in the cited references may have a lower number of pluripotent cells, all the claims require is that these cells be present in the treated population. There is no reason to expect that such cells are not present in the types of cell cultures used by the references cited, since these are the same types of cells used by Applicant, even if Applicant's experiments enrich for the subpopulation of these cells found within the population of cells used by the cited references.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (571) 272-0759. The examiner can normally be reached on Monday-Thursday 7:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Lacourciere
June 1, 2004

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER